Please add the following new claims.

120. (New) The aerosol composition of claim 14, wherein the drug is selected from the group consisting of beclomethasone dipropionate, naproxen, triamcinolone acetonide, budesonide, and an anti-emetic.

121. (New) The aerosol composition of claim 25, wherein the drug is selected from the group consisting of beclomethasone dipropionate, naproxen, triamcinolone acetonide, budesonide, and an anti-emetic.

REMARKS

Applicants and their counsel thank Examiners Ware and Kishore for the productive interview conducted on May 30, 2002, the subject matter of which is incorporated into the present response. Applicants respectfully request reconsideration of this application in view of the foregoing amendments and in view of the reasons which follow.

I. Status of the Claims

Following entry of this amendment, claims 11 – 36, 40 – 45, 47 – 49, 51 – 59, 61, 63, 65, 67, 69, and 70 – 121 are pending.

Claim 90 was amended to delete the recitation of a bronchodilator, a corticosteroid, and an anti-fungal to harmonize this claim with claims 14, 25, 71, 73, 75, 77, 79, 81, 83, 97, 104, and 111, which were similarly amended in the previous Response.

Additionally, claims 97, 104, and 111 were amended to correct the antecedent basis of the claims. Claim 119 was amended to depend from claim 90. Finally, claims 120 and 121 were added to recite drugs specifically disclosed in the working examples. Support for claims 120 and 121 can be found in Examples 1 and 2 (beclomethasone dipropionate); Examples 3 and 4 (naproxen); Examples 5, 8A, and 9B (triamcinolone acetonide); Examples 6 and 9A (budesonide); and Examples 7, 7A, and 7B (an anti-emetic).

Applicants acknowledge that the foregoing amendments are submitted after final rejection of the claims. However, because the amendments do not introduce new matter, and because the amendments either place the application in condition for allowance or at least in better condition for appeal, entry thereof by the Examiner is courteously requested.

II. Rejections Under 35 U.S.C. § 103(a)

A. Edwards et al.

Claims 11 – 34, 40, 41, 44 – 45, 47, 48, 51 – 62, 69 – 96, and 111 – 119 stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Edwards et al. (U.S. Patent No. 5,985,309; "Edwards").

1. The Examiner's Basis for the Rejection

The Examiner reiterated his previous allegations that Edwards discloses, *inter alia*, "aerosol particle compositions that are less than 100 μm in diameter and which have surfactants adsorbed thereon." Office Action at page 2. Referring to Example 14 of Edwards, the Examiner further alleged that the "compositions of the instant claims and those of [Edwards] do not appear to be different." *Id.*

The Examiner acknowledged that the present claims require drug particles to have an effective average particle size of less than about 1 μm, meaning that at least 50% of the drug particles have a particle size of less than about 1 μm. However, the Examiner maintained the rejection because some particles of Applicants' invention "*may* be 100 nm while some *may* be 10 microns." Office Action at page 5 (emphasis added). Continuing, the Examiner alleged that Edwards "teaches particles having a mass-mean true diameter of about 2 microns," and that the particles of Edwards "may be from 200 microns [*sic*] and some may be 20 microns." Citing *Titanium Metals Corp. of America v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985), the Examiner alleged a *prima facie* case of obviousness because the range of particle sizes taught by Edwards overlaps, or is close to, the claimed range such that a person skilled in the art would expect the particles of Edwards to exhibit the same properties – effective delivery to both the upper and deep lung – as do the claimed particles. Applicants respectfully traverse this ground for rejection.

2. Edwards Does Not Teach or Suggest the Claimed Drug Particle Size

The claimed invention recites two distinct particle sizes: (1) the particle size of the drug, which is less than about 1 μm; and (2) the particle size of the dry powder aggregates of the nanoparticulate drug particles, which is less than or equal to about 100 μm. Applicants' claims require that 50% of the drug particles in a composition have a particle size of less than 1 micron. This is not taught or suggested by Edwards.

Specifically, Edwards teaches particulate compositions having a mean geometric diameter of between 5 μm and 30 μm. *See e.g.*, Edwards at col. 5, lines 10 – 13. In addition, in the Examples Edwards refers to compositions having a mean particle size of 2 microns. Thus, Edwards does not disclose drug particle compositions having a particle size as claimed in the present invention.

The *Titanium Metals* court, upon which the Examiner relies, held that the proportions of an alloy actually disclosed by the prior art were so close to the claimed alloy proportions that a person of skill in the art would expect the claimed and the prior art alloys to *possess the same properties*. *See Titanium Metals Corp. of America v. Banner*, 778 F.2d 775, 779, 227 USPQ 773 (Fed. Cir. 1985). Consequently, the alloy itself was deemed to be *prima facie* obvious. *Id.* But the facts before the *Titanium Metals* court are distinguished from those in the present case, as in the present case *the properties* of the compositions of Edwards and of the claimed invention are different because the compositions require different active agent particle size distributions.

It is the nanoparticulate size of the active agent particles which results in superior drug delivery. For example, Applicants' specification teaches that "[c]onventional micronized drug particles of 2-3 microns in diameter are often difficult to meter and disperse in small quantities because of the electrostatic cohesive forces inherent in such powders. These difficulties can lead to loss of drug substance to the delivery device as well as incomplete powder dispersion and sub-optimal delivery to the lung." *See* page 16 of the application. In addition, Applicants teach that the dry powder aerosols of the invention contain nanoparticulate drugs that can be made smaller than comparable micronized drug substance, resulting in more efficient delivery to the lung (particularly the deep lung), and that aggregates of nanoparticulate drugs are spherical in geometry and have good flow properties, thereby aiding in dose metering and deposition of the administered composition in the lung or nasal cavities. *See* page 17 of the application. Finally, Applicants teach that the nanoparticulate drug dry powder aerosols of the invention produce a more complete absorption and rapid onset of action. *See* page 23 of the application. All of these advantages flow from the nanoparticulate particle size of the active agent.

Because Edwards does not teach the drug particle sizes of the claimed invention, and because the smaller drug particle sizes of the claimed invention impart useful benefits over the compositions of Edwards, the claimed invention is patentable over Edwards.

No 1Dec comparing Edwards

3. Edwards Teaches Away From the Claimed Invention, as the Reference Teaches that Large Drug Particles of Low Density are Preferred to Avoid Macrophage Engulfment

In addition to failing to teach Applicants' claimed drug particle size, Edwards teaches *away* from the claimed invention in that the reference states that *larger and less dense* particles are preferred to avoid macrophage engulfment of the active agent:

> In comparison to smaller, relatively denser particles, the larger (at least about 5 μm) aerodynamically light particles also can potentially more successfully avoid phagocytic engulfment by alveolar macrophages and clearance from the lungs, due to size exclusion of the particles from the phagocytes' cytosolic space. Phagocytosis of particles by alveolar macrophages diminishes precipitously as particle diameter increases beyond 3 μm.

See col. 10, lines 17-22, of Edwards.

a. Edwards Discloses Amorphous and Aerodynamically Light Drug Particles

The particles disclosed by Edwards comprise aerodynamically light particles having preferred tap densities of less than 0.4 g/cm^3. *See* Edwards at col. 3, line 65 – column 4, line 1). Here, "aerodynamically light" refers to a property of particles having low densities such that their aerodynamic diameters are numerically much smaller than their geometric diameters (e.g., an aerodynamic diameter of 1-5 μm vs. a geometric diameter of 5-30 μm). *See* Edwards at col. 4, lines 1 – 7. Edwards describes several methods of manufacturing the particles, including emulsion solvent evaporation and spray drying, which are precipitation techniques resulting in amorphous drug substances. *See* Edwards at Examples 1 and 2, respectively. Thus, as shown in these examples, the aerodynamic lightness is achieved because the resultant particles are highly porous and have densities of approximately 0.4 g/cm^3 or less.

Edwards also discloses that "the particles can be prepared entirely from a therapeutic or diagnostic agent, or from a combination of the agent and a surfactant." Edwards at col. 5, lines 50-52. Therapeutic agents that are exemplified by Edwards include testosterone (*see* Example 2), estradiol (*see* Example 5), and albuterol (*see* Example 10). All three of these drug substances can exist as crystalline materials with densities of 1.18 (*see* Ohrt *et al.* and Thakkar *et al.*; Exhibit 1), 1.17 (*see* Ohrt *et al.*; Exhibit 2), and 1.15 g/cm^3 (*see* Beale *et al.*; Exhibit 3), respectively.

Additionally, Edwards discloses particles that comprise diagnostic agents such as "iodine based materials . . . typified by diatrizoate and iothalmate . . ." *See* Edwards at col. 13, lines 4 – 6. Such diagnostic agents contain heavy (i.e., X-ray absorbing) atoms which result in the *crystalline* diagnostic agents having densities that are often greater than 2.0 g/cm^3. For example, the density of the ethyl ester of diatrizoic acid is 2.30 g/cm^3.

Taking the densities of crystalline therapeutic and diagnostic agents into account, together with the teaching of Edwards that the aerodynamically light particles have densities of 0.4 g/cm^3 or less, one of ordinary skill in the art would readily infer that the particles of Edwards comprise drug substances that are *amorphous* and highly porous. Thus, the aerodynamically light particles of Edwards could not be crystalline, in contrast to the claimed invention, because this dense, ordered physical state is wholly inconsistent with aerodynamic lightness.

b. The Claimed Particles are Crystalline and Aerodynamically Heavy

In contrast to the amorphous particles of Edwards, the nanoparticulate particles of the claimed invention comprise crystalline drug substances. Furthermore, the densities of the claimed particles are greater than or equal to 1 g/cm^3 in view of the densities exhibited by typical organic crystalline materials, such as testosterone, estradiol, albuterol, and the ethyl ester of diatrizoic acid discussed above. Thus, the aerodynamic diameters of the claimed particles are approximately equal to the geometric diameters because the particles are not substantially porous and comprise crystalline drug substance.

Therefore, not only does Edwards fail to teach the claimed invention, but Edwards also fails to provide any motivation to modify the teaching of Edwards to obtain the claimed invention. Armed with the teaching of Edwards that larger drug particles of low density are preferred to avoid macrophage engulfment of the active agent, one of ordinary skill in the art at the time that the claimed invention was made would not have been motivated to make the particles of Edwards more dense, crystalline, and smaller such that at least 50% of the particles were less than about 1 micron.

For at least these reasons, Edwards does not teach or suggest the claimed invention and, therefore, withdrawal of this ground for rejection is respectfully requested.

B. Edwards in View of Liversidge et al. Do Not Teach or Suggest The Claimed Invention

Claims 11 – 34, 40 – 45, 47, 48, 51 – 62, 65 – 96, and 97 – 119 stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Edwards in view of Liversidge et al. (U.S. Patent No. 5,145,684; "Liversidge"). Office Action at page 3. Applicants courteously traverse this ground for rejection.

1. The Examiner's Basis for the Rejection

The Examiner indicated that Liversidge teaches drug particle compositions that are less than 100 μm in diameter, that have a surface modifier adsorbed thereon, and that are used for the administration of drugs such as corticosteroids. Additionally, the Examiner alleged that Liversidge teaches a method of producing particles by a milling procedure, after which the particles are separated from the resultant dispersion by using a "sedimentation field flow fractionator", thereby yielding particles that appear to be "the same as those of the instant claims."

The Examiner concluded that, "absent a demonstration between using a sedimentation field flow fractionator and evaporation," it would have been obvious for a person of ordinary skill in the art to combine the teachings of Edwards and Liversidge to arrive at the present claimed aerosol particle formulations.

2. Edwards Does not Teach or Suggest the Claimed Drug Particle Size

Edwards fails to meet the limitations of the claimed invention for the reasons set forth above, as Edwards does not teach or suggest aerosol compositions comprising crystalline nanoparticulate drug particles of about 1 μm or less.

3. Liversidge Does not Remedy the Deficiencies of Edwards

Liversidge does not disclose aerosol dosage forms of nanoparticulate drugs . For example, Liversdige teaches the following:

> It is contemplated that the pharmaceutical compositions of this invention will be particularly useful in oral and parenteral, including intravenous, administration applications. It is expected that poorly water soluble drug substances, which prior to this invention, could not have been administered intravenously, may be administered safely in accordance with this invention. Additionally, drug substances which could not have been administered orally due to poor bioavailability may be effectively administered in accordance with this invention.

See Liversidge at col. 8, lines 10 – 20. Thus, the claimed invention is a substantial improvement over the invention of Liversidge as it has now been discovered that nanoparticulate drugs can be effectively incorporated into aerosol dosage forms, including dry powder aerosol dosage forms.

This discovery was unexpected because aerosol dosage forms can be extremely difficult to design. For example, Edwards teaches that difficulties for the aerosol delivery of macromolecules include:

> protein denaturation during aerosolization, excessive loss of inhaled drug in the oropharyngeal cavity (often exceeding 80%), poor control over the site of deposition, lack of reproducibility of therapeutic results owing to variations in breathing patterns, the frequent too-rapid absorption of drug potentially resulting in local toxic effects, and phagocytosis by lung macrophages.

See Edwards at col. 1, lines 33 – 42.

Moreover, prior to Applicants' invention, it was not known whether liquid formulations of nanoparticulate drugs could be processed into dry powder aerosols of nanoparticulate drugs having suitable aerodynamic properties.

This is significant in that a primary challenge that must be overcome in the preparation of many dry powder aerosols is the avoidance of particulate aggregation, which is caused by particle-particle interactions, such as hydrophobic, electrostatic, and capillary interactions. An effective dry-powder inhalation therapy for both short and long term release of therapeutics, either for local or systemic delivery, requires a powder that displays minimum aggregation, as well as a means of avoiding or suspending the lung's natural clearance mechanisms until drugs have been effectively delivered. *See* Edwards at col. 3, lines 22 – 30.

Such difficulties in designing aerosol dosage forms of dry powder drug compositions, which were well known in the art at the time the claimed invention was made, would have made one of

ordinary skill in the art unable to make the claimed compositions with any reasonable expectation of success, given the teachings of Edwards and Liversidge.

4. The Examiner's Comments Regarding Sedimentation Field Flow Fractionation

The Examiner maintained that a combination of Edwards and Liversidge renders the claimed invention obvious "absent a demonstration between using a sedimentation field flow fractionator and evaporation." Office Action at page 4.

It appears that the Examiner is asserting that sedimentation field flow fractionation, as taught by Liversidge, is a process in which particles are extracted or isolated, and that this process could be used in conjunction with Edwards to obtain an aerosol composition having Applicants' claimed particle size. Applicants courteously point out that a sedimentation field flow fractionator is employed to *measure* particle size, and does not refer to a method of obtaining small particles. *See* Liversidge at col. 5, lines 20 – 24.

Edwards teaches an aerosol having particles larger than that claimed by Applicants, and Edwards teaches that such larger particles are preferred. Liversidge does not remedy the deficiency of Edwards, as referencing a well known technique of measuring particle size does not teach or suggest modifying the composition of Edwards to obtain a small particle composition, as claimed by Applicants. For at least this reason, Edwards in view of Liversidge does not teach or suggest the claimed invention. Applicants respectfully request that this ground for rejection be withdrawn.

C. The Claimed Invention is not Taught or Suggested by Edwards in View of Dalby et al.

Claims 35, 36, 49, 63, and 64 stand rejected under 35 U.S.C. 103(a) as being allegedly unpatentable over Edwards in view of Dalby et al. (U.S. Patent No. 5,202,110; "Dalby"). Applicants respectfully traverse this ground for rejection.

1. The Examiner's Basis for the Rejection

Dalby discloses formulations for the delivery of a certain drug in pMDI's containing non-chlorofluorocarbon ("non-CFC") propellants. The Examiner asserted that it would have been obvious to one of ordinary skill in the art to combine the drug particle compositions of Edwards with the non-CFC propellants of Dalby to obtain Applicants' claimed aerosol compositions. Applicants respectfully disagree.

2. Dalby Does Not Remedy the Deficiencies of Edwards

As discussed above, Edwards does not teach or suggest aerosol compositions comprising crystalline nanoparticulate drug particle of about 1 micron or less. Dalby fails to remedy this deficiency. Thus, Edwards in combination with Dalby does not teach or suggest the claimed invention. Accordingly, withdrawal of this ground for rejection is respectfully requested.

III. Conclusion

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

If there are any fees due in connection with the filing of this Amendment, please charge the fees to our Deposit Account No. 19-0741. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

Date July 11, 2002

By Michele M Simkin

FOLEY & LARDNER
Washington Harbour
3000 K Street, N.W., Suite 500
Washington, D.C. 20007-5143
Telephone: (202) 672-5538
Facsimile: (202) 672-5399

Michele M. Simkin
Attorney for Applicant
Registration No. 34,717

Marked-Up Version of Amended Claims to Show Changes Made

90. (Amended) The method of claim 40, wherein the drug is selected from the group consisting of proteins, peptides, [bronchodilators, corticosteroids,] elastase inhibitors, analgesics, [anti-fungals,] cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, fungal infection therapies, and respiratory illness therapies associated with acquired immune deficiency syndrome, an oncology drug, an anti-emetic, [an analgesic,] and a cardiovascular agent.

97. (Twice Amended) The [aerosol composition] method of claim 42, wherein the drug is selected from the group consisting of proteins, peptides, elastase inhibitors, analgesics, cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, fungal infection therapies, and respiratory illness therapies associated with acquired immune deficiency syndrome, an oncology drug, an anti-emetic, and a cardiovascular agent.

104. (Twice Amended) The [aerosol composition] method of claim 43, wherein the drug is selected from the group consisting of proteins, peptides, elastase inhibitors, analgesics, cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, fungal infection therapies, and respiratory illness therapies associated with acquired immune deficiency syndrome, an oncology drug, an anti-emetic, and a cardiovascular agent.

111. (Twice Amended) The [aerosol composition] method of claim 44, wherein the drug is selected from the group consisting of proteins, peptides, elastase inhibitors, analgesics, cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, fungal infection therapies, and respiratory illness therapies associated with acquired immune deficiency syndrome, an oncology drug, an anti-emetic, and a cardiovascular agent.

119. (Amended) The method of any one of claims 90, 97, 104, or 111 wherein the drug is an anti-fungal.